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Accelerated Reversal of Atracurium Blockade with Priming Doses of Edrophonium

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Recently, we demonstrated that administration of neostigmine in divided doses, produced a significantly faster reversal of residual atracurium-induced neuromuscular blockade compared to the rate of reversal following a single bolus administration.¹

This phenomenon may not be unique to neostigmine and may be common to other acetylcholinesterase inhibitors. The purpose of this study was, therefore, to investigate the reversal characteristics following administration of edrophonium in divided doses.

PATIENTS AND METHODS

After institutional approval, 22 ASA physical status I or II adult patients undergoing minor elective procedures were studied. All patients were free from neuromuscular, renal, or hepatic disease and were not taking any drugs known to interfere with neuromuscular function. Informed consent was obtained. All patients were premedicated with 0.15 mg · kg⁻¹ diazepam orally 90 min preoperatively.

An intravenous infusion of lactated Ringer's solution in 5% dextrose was established prior to induction. The EKG and nasopharyngeal temperature were monitored continuously by a Medishield M1 monitor. Blood pressure was measured every 5 min by an electronic oscillotonometer (DINAMAP®).

In all patients, anesthesia was induced with fentanyl 2 µg · kg⁻¹ thiopental 5 mg · kg⁻¹, and was maintained with 70% nitrous oxide in oxygen and halothane (0.5–1.0%). Ventilation was adjusted to maintain normocapnia, and end tidal CO₂ was monitored by a Datex infra-red CO₂ analyzer.

The ulnar nerve was stimulated at the wrist with square wave supramaximal stimuli of 0.2 ms duration, delivered

in a train-of-four (TOF) sequence at 2 Hz every 10 s, using a Myotest peripheral nerve stimulator (Biometer®). The resultant contraction of adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000 Biometer).² Preload tension on the thumb was maintained at 300 g throughout the investigation.

After stabilization of twitch recording, atracurium 0.5 mg · kg⁻¹ was administered and tracheal intubation was performed at maximum block. Patients were excluded from the study if incremental doses of atracurium were administered.

At the end of surgery, when spontaneous recovery had begun and the first twitch (T1) of the TOF returned to 10% of the control value, patients were randomly allocated into two groups. In Group I, edrophonium 1 mg · kg⁻¹ was administered in a single bolus dose preceded by 0.02 mg · kg⁻¹ atropine. In group II, an initial dose of edrophonium 0.2 mg · kg⁻¹ was administered followed 3 min later by 0.8 mg · kg⁻¹. In the latter group, 0.5 mg atropine was administered before the first dose of edrophonium, and the remainder of the atropine was administered before the second dose of edrophonium. The same total dose of edrophonium 1 mg · kg⁻¹ and atropine 0.02 mg · kg⁻¹ was administered to all patients. Patients continued to inhale 70% nitrous oxide in oxygen and 0.5–1% halothane until all measurements were complete. Antagonism of block was considered adequate when a TOF ratio (the amplitude of the fourth to the first evoked response; T₄/T₁) of 0.75 was attained.³ Further assessment of the patients was carried out in the recovery room for 60 min using clinical criteria, such as the ability to open eyes, cough, and sustain a head lift.

The following parameters were calculated: (a) onset time following full dose of edrophonium in Group I and the two (first and second) doses of edrophonium in Group II, was the time from injection of the antagonist until the first increase of the twitch was observed; (b) T1 and TOF ratio in Group I, 3 min after the administration of edrophonium 1 mg · kg⁻¹; (c) T1 and TOF ratio in Group II, 3 min after administration of the initial dose of edrophonium 0.2 mg · kg⁻¹ (just before the administration of the second dose); (d) time for the twitch height (T1) to recover from 25 to 75% of control (recovery index); (e) reversal time was the time taken from the first injection of the drug until the TOF ratio value had reached 0.75;

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TABLE 1. First Twitch (T1) and Train-of-four (TOF) Ratio 3 Min after the Administration of Edrophonium, Recovery Index and Reversal Time

	3 Min After the First Administration of Edrophonium*		Recovery Index† (S)	Reversal Time‡ (S)
	T1 (% of Control)	TOF Ratio		
Group I (n = 11) Single dose	84.7 ± 15.8	0.56 ± 0.07	137.2 ± 108.6	627.2 ± 215.4
Group II (n = 11) Divided dose	80 ± 10.4	0.46 ± 0.07	111.8 ± 45	250 ± 45.2
P	NS	0.006	NS	0.00007

* Just before the administration of the second dose of edrophonium to Group II.

† Recovery index was the time from 25 to 75% recovery of T1.

‡ Reversal time was the time taken from the first injection of edrophonium until the TOF ratio value had reached 0.75.

and (f) the TOF ratio at 10% increments of T1 tension recovery.

STATISTICS

The results in the two groups were compared using Student's *t* test for two independent samples. A *P* value of less than 0.05 was considered statistically significant.

The values for every other TOF ratio in each group were utilized for linear regression analysis. TOF was regressed on time in each group. An array of 11 values of TOF corresponding to each time facilitated testing for linearity, normality, and equality of variances. Normality and equality of variances in the subpopulations of TOF at different times were obvious in both groups, but the ANOVA test for linearity indicated a valid linear statistical model for Group I only. Other forms of non-linear regression were tried for Group II, but none yielded a valid model. Inspection of the scatter diagram in Group II suggested two line segments, one for the time interval between 60–180 s and a second from 220–300 s after first administration of edrophonium to this group. During the 40-s period (between 180–220 s) following the administration of the second dose of edrophonium (*i.e.*, the

interval between the two line segments) a significantly faster rate of recovery of the TOF ratio had occurred. A paired *t* test was performed to assess the recovery of TOF ratio during this period of time in Group II. The linearity was tested for each line segment again by ANOVA technique and both segments were found to be very much linear. Also, the test of equal slopes was performed for both line segments, and indicated very little and insignificant difference. The common slope for the two line segments was then estimated by the weighted average method and tested for equality with the slope in Group I.⁴

RESULTS

All results are expressed as mean ± SD. There was no significant difference between the groups regarding the patients' age, sex, or weight. The mean age was 28.9 ± 5.6 and 27.3 ± 5.6 yr, and mean body weight was 63.1 ± 7.9 and 57.1 ± 9 kg in Groups I and II, respectively. The male/female ratio was 8/3 and 7/4 in Groups I and II, respectively.

The mean onset time following the administration of edrophonium 1 mg · kg⁻¹ in Group I was 20.4 ± 6.8 s. In Group II, the mean onset times following administration of the first and second dose of the antagonist were 32.1 ± 12.7 and 15.7 ± 5.8 s, respectively.

Three minutes after the administration of edrophonium 0.2 mg · kg⁻¹ in Group II (just before the administration of the second dose of edrophonium), the mean TOF ratio was 0.46. This was significantly less (*P* = 0.006) when compared to 0.56, the mean TOF ratio attained 3 min after the administration of edrophonium 1 mg · kg⁻¹ in Group I (table 1). However, there was no significant difference in the degree of recovery of T1 in the two groups at that time (table 1). The 25–75% recovery time of T1 was not significantly different in both groups (table 1).

Administration in divided doses resulted in a significantly (*P* = 0.00007) faster recovery of the TOF values as assessed by the reversal time (fig. 1).

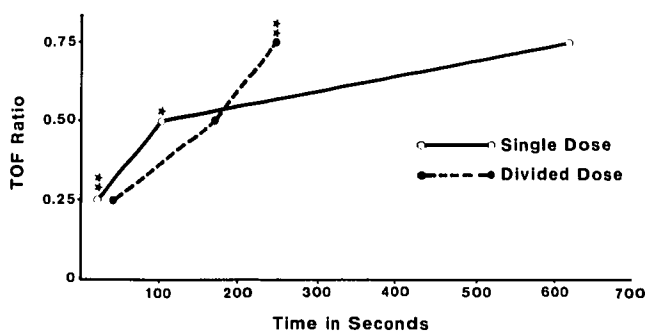


FIG. 1. Recovery of the train-of-four (TOF) ratio after edrophonium administration in single (n = 11) or divided doses (n = 11). ★ *P* < 0.01; * *P* < 0.001.

There was no significant difference in the mean values of the TOF ratios for 10% increments of T1 tension between the two groups.

The estimated linear equation that describes the relationship between the TOF ratios and time in Group I was:

$$y = 0.449471 + 0.000503 x, \quad (r = 0.72)$$

where "y" represents TOF ratio and "x" represents the time. The common slope estimated in Group II was found to be 0.001231. Statistical analysis yielded a highly significant difference ($P = 5 \times 10^{-11}$) between the estimated common slope in Group II and the slope in Group I. This indicates that the rate of TOF ratio recovery following administration in divided doses was significantly faster (fig. 1) than that following single bolus administration, although the 40-s period (from 180–220 s) following the administration of the second dose of edrophonium in Group II (where the fastest rate of recovery had occurred) was not included in this analysis. This rate of recovery resulted in highly significant TOF value ($P = 1.7 \times 10^{-8}$), 40 s after administration of the second dose of edrophonium to Group II, when compared to the mean TOF ratio value just before the injection (0.71 ± 0.04 and 0.46 ± 0.07 , respectively). Furthermore, the mean changes in the TOF ratio during this 40 s was 0.25 ± 0.04 in Group II; this was significantly greater ($P = 3.65 \times 10^{-9}$) than the 0.02 ± 0.01 , which is the mean changes in the TOF ratio occurred in Group I during the same period of time.

DISCUSSION

In the present study, when edrophonium was administered in divided doses, the rate of recovery of neuromuscular function was significantly faster after the administration of the second dose in Group II, as evidenced by the marked difference between the slopes of the regression lines ($P = 5 \times 10^{-11}$). This acceleration resulted in a significantly shorter reversal time.

Although one would expect that antagonist priming would work if time to total reversal were measured from the administration of the second dose of edrophonium, one does not, however, expect faster reversal with divided doses if time to reversal is measured from the administration of the first dose. This phenomenon has been demonstrated before with neostigmine,¹ and can be explained on the basis of recent work⁵ on the kinetics of erythrocyte cholinesterase, the properties of which are very similar to neuromuscular junction cholinesterase.⁶ It was found that facilitation of twitch height did not occur when erythrocyte cholinesterase was inhibited less than 85%. Between 85 and 98% inhibition, facilitation was linearly related to enzyme inhibition.⁵ Therefore, a large proportion of the acetylcholinesterase could be inhibited

without effect on neuromuscular function.[§] This suggests a "margin of safety" in enzyme inhibition⁷ similar to that seen during blockade of neuromuscular transmission by non-depolarizing muscle relaxants.⁸ By analogy to the priming principle,⁹ the initial relatively small dose of edrophonium will cause partial enzyme inhibition and, therefore, will decrease the margin of safety of acetylcholinesterase enzyme, allowing a more pronounced effect of the second dose.

Bowman¹⁰ suggested that depression of T1 and the TOF fade are independent effects of acetylcholine antagonists; the former is the result of postjunctional block, whereas the latter arise from the action on prejunctional receptors. Edrophonium is known to have a marked presynaptic activity.^{11,12} In the present study, the effect of antagonist (edrophonium) on the relationship between TOF fade and first twitch depression was examined. There was no difference in the mean values of the TOF ratios for 10% increments of T1 tension during antagonism between the two groups studied. In contrast, during atracurium-induced blockade, administration of neostigmine $0.04 \text{ mg} \cdot \text{kg}^{-1}$ 3 min after an initial dose of $0.01 \text{ mg} \cdot \text{kg}^{-1}$ of the drug at 10% spontaneous recovery of twitch height resulted in a significantly higher TOF ratios at T1 twitch heights ranging from 90–100% of control.¹

Variability in response was evident following bolus administration of edrophonium in Group I, as demonstrated by the larger standard deviations. This finding is in agreement with results of other investigators.^{13–15} However, in addition to the significant acceleration of the recovery of neuromuscular function, administration of edrophonium in divided doses did not result in any variability regarding the edrophonium's ability to reverse profound neuromuscular blockade following atracurium.

The hypothesis that administration of anticholinesterases in divided doses will markedly shorten the reversal time of atracurium was clearly demonstrated in this study, as in the previous one.¹ The results of this study, when compared with our previously reported results with neostigmine,¹ demonstrate that following a single bolus administration, mean reversal time (\pm SD) to a TOF ratio of 0.75 was significantly shorter following neostigmine $0.05 \text{ mg} \cdot \text{kg}^{-1}$ than after edrophonium $1 \text{ mg} \cdot \text{kg}^{-1}$ (468.6 ± 150.3 and 627.2 ± 215.4 s, respectively). This is in accord with the results reported by Rupp *et al.*¹⁴ that neostigmine antagonizes a profound neuromuscular block induced by atracurium more rapidly than does edrophonium. However, following administration of the antagonist in divided doses, reversal time was significantly faster following edrophonium than after neostigmine (250

§ Cronnelly R: Kinetics of Anticholinesterases. *Clinics in Anesthesiology* 3:315–328, 1985

± 45.2 and 391.8 ± 83.3 s, respectively). The reason for this apparent difference between edrophonium and neostigmine is unknown. It is known that inhibition of the cholinesterase enzyme by edrophonium occurs by a different mechanism from that of neostigmine.¹⁶ Although there is still some controversy concerning the mechanism of anticholinergic action of edrophonium and neostigmine,[§]^{17,18} cholinesterase inhibition appears to be a major factor.[§]

Three questions, however, have to be answered before recommending the routine clinical application of this maneuver. First, what is the optimal time interval between the first (priming) and the second dose of the acetylcholinesterase inhibitor? Secondly, what is the optimal priming dose? Lastly, what is the optimal size of the second dose?

We conclude that, compared with a single bolus, administration of edrophonium $0.2 \text{ mg} \cdot \text{kg}^{-1}$ followed 3 min later by $0.8 \text{ mg} \cdot \text{kg}^{-1}$ significantly accelerated the rate of reversal of residual atracurium-induced neuromuscular blockade. With this sequence of administration, about 4 min were necessary to obtain a TOP ratio of 0.75 when antagonism of atracurium paralysis was attempted at 90% depression of twitch height.

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Intrathecal Morphine in Conjunction with a Combined Spinal and General Anesthetic in a Patient with Multiple Sclerosis

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Selecting an anesthetic management plan for patients with multiple sclerosis can be difficult. General anesthesia is usually recommended, while spinal anesthesia is dis-

couraged. In this report, spinal anesthesia supplemented with inhaled general anesthetics were used successfully in a patient with multiple sclerosis. In addition, we describe the first reported use of intrathecal morphine in a patient with this disease.

REPORT OF A CASE

A 53-yr-old male with impotence related to long-standing multiple sclerosis presented for elective insertion of an inflatable penile pros-

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